Effect of raised plasma β endorphin concentrations on peripheral pain and angina thresholds in patients with stable angina

N F Jarmukli, J Ahn, A Iranmanesh, D C Russell

Abstract

***Objective*—To determine whether changes in plasma concentrations of β endorphins alter angina threshold and peripheral pain threshold in patients with stable angina.**

***Design*—Latin square design comparison of angina thresholds by exercise treadmill test and peripheral pain thresholds using a radiant heat source in eight patients with stable angina under control conditions, after stimulation of pituitary β endorphin release by ketoconazole, after suppression of pituitary β endorphin release by dexamethasone, and after blockade of opioid receptors by intravenous naloxone.**

***Results*—An approximately fivefold increase in circulating concentrations of β endorphins was found after administration of ketoconazole (mean (SEM): 13.9 (1.2) *v* 73.8 (6.2) pg/ml; $p < 0.05$), which was associated with an increase in peripheral pain threshold to a radiant heat source (time to onset of pain perception 72 (19) *v* 123 (40) seconds; $p < 0.05$), but no significant difference in angina threshold. A reduction in circulating concentrations of β endorphins after pretreatment with dexamethasone was statistically non-significant (13.9 (1.2) *v* 9.0 (1.5) pg/ml; NS) and was not associated with any change in either peripheral pain or angina thresholds. No effects were seen after blockade of opioid receptors by previous administration of intravenous naloxone.**

***Conclusions*—Increased plasma concentrations of β endorphins alter peripheral pain threshold but not angina threshold in patients with stable angina pectoris.**

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It is well established that both somatic pain perception and angina threshold in patients with obstructive coronary artery disease can be modified by a variety of physiological factors and pharmacological interventions.[1] Multiple neural mechanisms may be involved, at the level of the peripheral nerve terminals, the spinal cord, brainstem, thalamus, hypothalamus, and cerebral cortex.[2–11] An important structure in pain signalling is the principal sensory nucleus of the thalamus.[12] In addition, descending neuronal pathways concerned with the modulation of visceral pain deriving from the heart are known to extend from the frontal cortex to the hypothalamus through the periaqueductal grey matter to the medulla and dorsal horn cells, where opioid mediated inhibition of nociceptive afferent signals may occur.[13–15] Abnormalities in nociceptive sensory gating mechanisms at the level of the thalamus have been reported in patients with silent ischaemia.[12] Endogenous opioids are intimately involved in the very complex functions of the so called "endogenous analgesia system" within the central nervous system, and effects of several opiate receptors (including μ, δ, κ, and σ) play a role.[16]

It has long been suggested, but never clearly established, that changes in circulating levels of endogenous opioid peptides, in particular β endorphins, may modulate both somatic and visceral pain perception by actions on the peripheral and central nervous system.[17–22] The aim of this study, therefore, was to determine whether controlled changes in circulating plasma β endorphin concentrations can alter angina pain threshold in patients with coronary artery disease, as assessed by exercise treadmill testing, and cutaneous somatic peripheral pain threshold, as determined by responses to a radiant heat source. An increase in plasma β endorphin concentration was achieved by the administration of ketoconazole, which stimulates pituitary release of β endorphin, and a reduction was achieved by administration of dexamethasone, causing central suppression of pituitary β endorphin release.[23]

Methods

PATIENTS

The study group comprised eight patients with a diagnosis of stable angina pectoris. All patients had a normal resting baseline ECG and evidence of symptomatic myocardial ischaemia on a previous abnormal diagnostic exercise treadmill test (with horizontal or downsloping ST segment depression, exceeding 1 mm, 0.08 seconds after the J point in two or more ECG leads), and typical symptoms of angina pectoris on exertion.

Patients were excluded if there was evidence of diabetes mellitus, myocardial infarction or unstable angina within the previous three months, congestive heart failure or cardiomyopathy, left ventricular hypertrophy, atrial fibrillation, alcohol abuse, or autonomic or peripheral neuropathy.

All antiangina agents with the exception of sublingual nitrates were discontinued for at least 48 hours, or for a period equivalent to five

plasma half lives of the drug, before the start of the study. No patients received steroid treatment, narcotic agents, or antifungal treatment within the six months of the study.

PROTOCOL

All subjects gave informed consent before participating in the study, according to the requirements of our institutional review board. In order to confirm the reproducibility of onset of angina symptoms during exercise testing in individual subjects, two successive preliminary exercise treadmill tests were performed at one week intervals, using a modified Balke protocol. Times to onset of angina pain and significant ST segment depression on the ECG (1 mm or more in two contiguous leads) were required to be within 15% of each other between successive tests for subjects to proceed in the study.

After completion of the preliminary exercise tests, all subjects underwent three further exercise treadmill tests, using the same modified Balke protocol, at one week intervals. All studies were performed after at least six hours in the fasting state and at the same times of day, in early afternoon.

Before each exercise test, subjects were assigned in random order—according to a Latin square design—to receive pretreatment with either dexamethasone (2 mg orally at midnight the night before), ketoconazole (1200 mg at midnight and 600 mg at 6 am), or naloxone (20 mg intravenously five minutes before exercise).

Venous blood was sampled from a peripheral arm vein at 30 minutes before and immediately before the onset of exercise, at peak exercise, and at 5, 10, 20, and 60 minutes after each period of exercise, for subsequent estimation of plasma concentrations of β endorphin, adrenocorticotrophic hormone (ACTH), and cortisol. Standard radioimmunoassay techniques were employed to measure hormone concentrations.

Angina threshold was defined as the time to onset of typical symptoms of angina during exercise treadmill testing. Anginal tolerance was defined as the total tolerated duration of exercise. Peripheral pain threshold was defined as the time to development of pain following exposure to radiant heat from a fibreoptic light source placed 1 cm over the skin of the forearm 2.5 cm proximal to the wrist. Pain threshold determinations were made in duplicate at 10 minute intervals before exercise and before withdrawal of blood for baseline hormone concentrations. Previous studies in eight normal subjects indicated that peripheral pain thresholds determined in this fashion were highly reproducible, with a coefficient of variation of 4.2%.

HORMONE ASSAYS

Plasma concentrations of β endorphin were measured in duplicate by radioimmunoassay (RIA), using reagents from Incstar Corporation (Stillwater, Minnesota, USA). In this assay, β endorphin was first extracted from plasma using specific absorption particles. The absorbed compound was then eluted from the particles and measured by radioimmunoassay. The minimum detectable amount of β endorphin by this assay was < 12 pg/ml, when defined as the apparent concentration at three standard deviations from the counts at maximum binding. The cross reactivity of this assay was less than 5% for β lipotropin and less than 0.01% for ACTH and melanocyte stimulating hormone (MSH). The intra-assay and interassay coefficient of variations are 9.1–13.7% and 18.1%, respectively, at plasma β endorphin concentrations ranging from 19.6 to 80 pg/ml. Plasma concentrations of ACTH were measured in duplicate by a two site IRMA (immunoradiometric assay) using reagents from Nichols Institute (San Juan Capistrano, California, USA). The assay sensitivity, defined as the smallest single value that can be distinguished from zero at the 95% confidence limit, was 1 pg/ml, with intra-assay and interassay coefficients of variation of 4.2–6.8% and 6.8–7.8%, respectively. The cross reactivity of this ACTH IRMA with β endorphin, thyroid stimulating hormone, luteinising hormone, follicle stimulating hormone, growth hormone, prolactin, and MSH was less than 0.1%. Plasma concentrations of cortisol were assayed in duplicate by solid phase RIA using reagents from Incstar Corporation. The sensitivity of the assay was 0.24 μg/dl and the intra-assay and interassay coefficients of variation were 2.7–4.5% and 5.2–9.7%, respectively.

STATISTICAL ANALYSIS

All numerical data are expressed as mean (SEM). Significance of changes in β endorphin concentrations and pain thresholds between study conditions was assessed using linear regression analysis with analysis of variance. Pearson correlations were used to assess the relation between continuous variables. A p value < 0.05 for two tailed testing was considered statistically significant.

Results

PATIENT POPULATION

Eight subjects completed all five exercise treadmill tests according to the protocol. All subjects were men, mean age 64 (9) years. All had evidence of significant coronary artery disease defined by a 75% or greater stenosis in one or more coronary vessels, confirmed by cardiac catheterisation. None had received antianginal, steroid, or opiate treatment for at least five plasma half lives of drug before each study.

HORMONAL RESPONSES

Changes in mean plasma concentrations of β endorphin, ACTH, and cortisol during and following exercise under each of the study conditions are illustrated in fig 1.

Under control conditions, mean plasma concentrations of β endorphins were low before exercise and did not rise significantly during or after exercise.

Ketoconazole administration resulted in an approximately fivefold increase in plasma concentrations of β endorphins (from 13.9 (1.2) to 73.8 (6.2) pg/ml; $p < 0.01$), which was sustained during and after exercise.

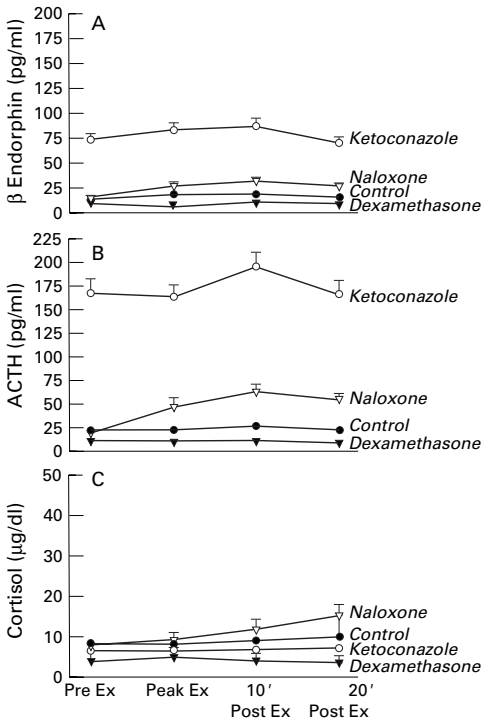

Figure 1 Plasma concentrations of β endorphin, adrenocorticotrophic hormone (ACTH), and cortisol before, during, and at 10 and 20 minutes after treadmill exercise in eight patients with stable angina, under control conditions (filled circles), and after pretreatment with ketoconazole (empty circles), dexamethasone (filled triangles), or naloxone (empty triangles). Error bars are SEM.

After dexamethasone pretreatment, mean plasma concentrations of β endorphins were reduced to about two thirds of control concentrations before exercise, and to about one half during and after exercise, although these changes did not attain statistical significance.

Similar changes were observed for mean plasma concentrations of ACTH, with an approximately eightfold increase in plasma ACTH after ketoconazole administration (from 21.2 (1.5) to 167.6 (15.1) pg/ml; $p < 0.05$) which was sustained during and after exercise, and a lowering of ACTH concentrations by approximately one half following dexamethasone (from 21.2 (1.5) to 11.2 (1.5) pg/ml), which did not attain statistical significance.

Significantly lower mean plasma concentrations of cortisol were found following administration of both ketoconazole (from 8.5 (0.9) to 6.7 (0.8) mg/dl, $p < 0.05$) and dexamethasone (from 8.5 (0.9) to 4.1 (2.0) mg/dl, $p < 0.05$). Trends towards higher mean plasma concentrations of both β endorphin and ACTH were observed after naloxone administration, but did not reach statistical significance.

Table 1 Anginal and peripheral pain thresholds, angina tolerance, and maximum workload achieved under control conditions and after pretreatment with ketoconazole, dexamethasone, and naloxone

	Control	*Ketoconazole*	*Dexamethasone*	*Naloxone*
Angina threshold (s)	254 (38)	282 (46)	226 (49)	246 (41)
Peripheral pain threshold (s)	72 (19)	123 (40)*	97 (39)†	110 (15)
Angina tolerance (s)	456 (62)	406 (43)	412 (46)	414 (67)
Workload (METS)	7.6 (0.8)	6.8 (0.6)	6.4 (0.5)	6.7 (0.6)

Data are mean (SEM).
*$r = 0.82$; $p < 0.02$ *v* control.
†$r = 0.72$; $p < 0.05$ *v* ketoconazole.

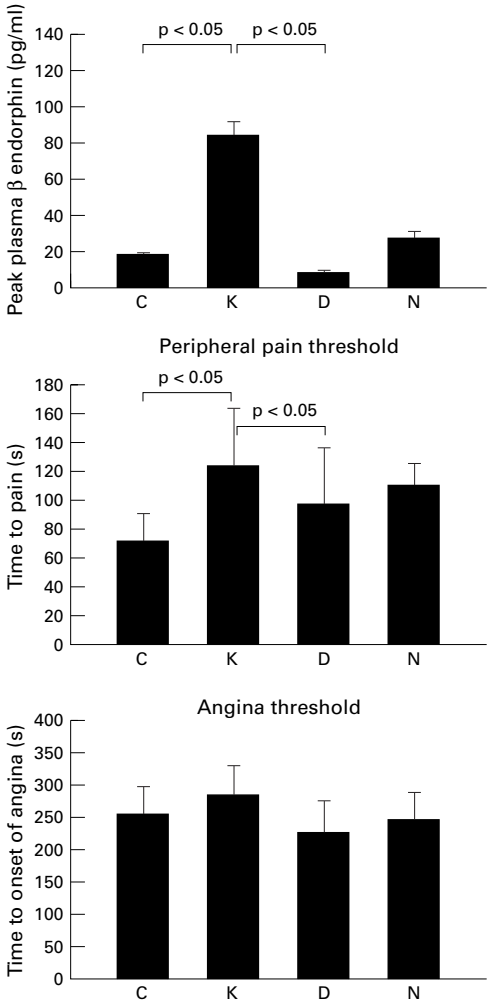

Figure 2 Plasma β endorphin concentrations at onset of angina (upper panel), peripheral pain thresholds (middle panel), and anginal thresholds (lower panel) during exercise treadmill testing in eight patients under control conditions (C), and after pretreatment with ketoconazole (K), dexamethasone (D), and naloxone (N). Error bars are SEM.

EXERCISE

No significant differences were found in the maximum workload achieved or total duration of exercise (angina tolerance) between any of the study conditions (table 1).

PERIPHERAL PAIN THRESHOLD

The time to onset of perceived somatic pain, determined by exposure to a radiant heat source, was highly reproducible between successive days under control conditions (mean time 72 (17) *v* 72 (19) seconds; NS), and was significantly prolonged after pretreatment with ketoconazole in comparison with control values (72 (19) *v* 123 (40) seconds; $r = 0.82$, $p < 0.02$; fig 2). This represented an 87.5 (37)% increase in the time to onset of pain after ketoconazole pretreatment (fig 3). No differences were observed in peripheral pain thresholds following dexamethasone pretreatment. A small increase in peripheral pain threshold was observed following naloxone pretreatment, but

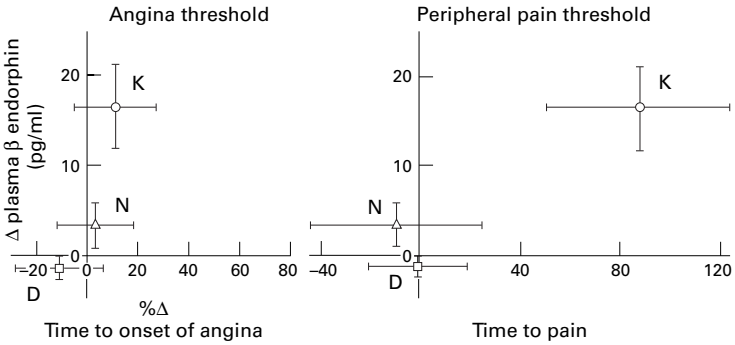

Figure 3 Relation between changes in plasma β endorphin concentrations and changes in angina threshold (left panel) and peripheral pain threshold (right panel) from control after pretreatment with ketoconazole (K), dexamethasone (D), or naloxone (N). Error bars are SEM.

this did not reach statistical significance (72 (19) *v* 110 (15) seconds; $r = 0.05$, NS).

ANGINA THRESHOLD

The angina threshold during treadmill exercise was not significantly changed following ketoconazole or dexamethasone pretreatment (fig 2 and table 1). Per cent differences in angina threshold following ketoconazole did not reach statistical significance (+11 (16)% change, NS; fig 3). No change in angina threshold was found following naloxone pretreatment (fig 3).

Discussion

To our knowledge this study is the first to address, in a controlled manner, the question of whether there is a direct effect of changes in endogenous circulating plasma β endorphins on peripheral pain and angina thresholds. Our findings suggest that increased concentrations of circulating plasma β endorphins under controlled conditions of repeat exercise treadmill testing are associated with an increase in peripheral pain threshold but not angina threshold in patients with stable angina. An approximately fivefold increase in plasma β endorphin was required to demonstrate the increase in peripheral pain threshold, which is within the expected range of physiological variation in β endorphin concentrations. No difference in either peripheral pain threshold or angina threshold was observed after blockade of opioid receptors using a high dose of the pharmacological opioid receptor blocking agent naloxone (20 mg intravenously) to ensure adequate pharmacological blockade of κ and δ opioid receptors in addition to the blockade of μ receptors achieved at lower doses of naloxone.[16]

MODULATION OF PLASMA β ENDORPHIN CONCENTRATIONS

We achieved wide physiological ranges of plasma β endorphin concentrations between successive study days by previous administration of either ketoconazole to stimulate, or dexamethasone to suppress, pituitary co-release of β endorphin and ACTH.[23 24] Ketoconazole is a potent inhibitor of adrenal cortisol production through inhibition of 11-β-hydroxylase and cholesterol side chain cleavage.[25] As anticipated, ketoconazole administration resulted in a fall in plasma cortisol concentrations and stimulation of the hypothalamic–pituitary axis manifested by an approximately fivefold increase in plasma β endorphin and a sevenfold increase in plasma ACTH concentrations. No additional significant changes in plasma β endorphin concentrations were observed during or following exercise in any of our subjects, in keeping with the short duration and relatively low intensity of the exercise employed. Although exercise stress can stimulate pituitary β endorphin release, this requires an exercise intensity of at least 70% of maximum over at least 15 minutes,[26] exceeding the anaerobic threshold and associated with lactate production.[27] In addition, more prolonged periods of submaximal exercise than used in our study would be required to cause the centrally mediated modulation of pain thresholds seen in experimental animals, which is associated with an increase in cerebrospinal fluid β endorphin concentrations without change in circulating β endorphin.[28] There was no indication in any of our subjects that pain itself, whether cardiac or peripheral, caused any secondary stimulation of pituitary β endorphin release or increase of plasma β endorphin concentrations.

EFFECTS ON PERIPHERAL PAIN THRESHOLD

Our findings indicate that increased concentrations of plasma β endorphins can increase peripheral pain thresholds at concentrations not associated with any detectable increase in angina threshold. Although it is clearly established that endorphic mechanisms are involved in peripheral pain perception, evidence for a direct modulatory effect of circulating plasma β endorphins has been largely circumstantial. Thus Marchant *et al* report that administration of naloxone causes reductions in electrical pain threshold and pain tolerance,[22] and Droste and Roskam[21] reported increased somatic pain thresholds in patients with silent ischaemia. Sheps *et al* reported an association between increased plasma β endorphin concentrations following the psychological stress of public speaking and peripheral pain threshold.[29] Possible mechanisms might include direct effects of circulating β endorphins on afferent nociceptive fibres or on cardiopulmonary baroreceptor afferents[30]; and they might involve influences on either the general somatic afferent pain signalling pathways which pass through the dorsal root cells to the spinothalamic tracts and the thalamic principal sensory nucleus,[7–11] or on a descending system extending from the frontal cortex and hypothalamus, through the periaqueductal grey matter, to the rostral ventromedial medulla and dorsal horn cells and the homologous trigeminal nucleus caudalis, where opioid inhibition of nociceptive signals may occur.[13–15] At the spinal level, ablation studies indicate that the control of nociceptive signal processing is influenced by the local action of opioids and by local feedback mechanisms.[15] The magnitude of any effect of circulating β endorphin may be restricted, however, by limitations in crossing the blood–brain barrier. Circulating plasma β

endorphins appear not to be related to so called "stimulation produced" analgesia pathways, the function of which remains intact after hypophysectomy and adrenalectomy and the removal of sources of circulating β endorphins and enkephalins.[31]

EFFECTS ON ANGINAL THRESHOLD

Our findings indicate that physiological increases in circulating concentrations of plasma β endorphins sufficient to increase peripheral pain threshold do not significantly influence anginal pain threshold. These findings would not preclude some possible very minor influence of plasma β endorphins on anginal threshold, although our data suggest that any such effect should be an order of magnitude less than the observed effects on somatic pain threshold, and demonstrable only with a very large sample size. Sylvén *et al* have shown that infusion of endogenous β endorphin, but not metenkephalin, counteracts the angina-like pain induced by bolus injections of adenosine.[32] Our data suggest that any such effect of endogenous β endorphin on true anginal pain perception would be less than 10%, and unlikely to be of clinical significance.

Other clinical studies addressing this question have been contradictory. Several studies are based on comparison of subjects with "silent" versus symptomatic ischaemia, but in whom functional differences in central nervous system pain perception and pain signalling pathways can be shown by positron emission tomography.[12] Thus, Marchant *et al* reported similar plasma concentrations of β endorphin and metenkephalin in these patient groups.[22] Glazier *et al* reported similar plasma concentrations of β endorphin, and metenkephalin in the basal state and during induction of forearm ischaemia in patients with varying tolerance to painless ischaemia.[33] Falcone *et al*,[17] however, reported plasma β endorphin concentrations in subjects with silent myocardial ischaemia that were approximately double those in patients with anginal symptoms, and suggest that increased concentrations of plasma β endorphins may indeed play a role in the decreased sensitivity to pain reported in these patients. This view is supported by Sheps *et al*,[18] who reported higher postexercise plasma β endorphin concentrations in patients with asymptomatic myocardial ischaemia, and a significantly positive correlation between postexercise endorphin concentrations and time to onset of angina. Such associations could equally be explained, however, on the basis of epiphenomena to more central opioid mechanisms.

Elucidation of the differing mechanisms of action of analgesic effects of endorphins on somatic and cardiac pain in angina pectoris clearly requires a better definition of the precise neural pathways for perception of cardiac and somatic pain. An important difference may be that while specific skin nociceptors have been identified which mediate peripheral pain perception, cardiac afferent sympathetic fibres with specific nociceptive endings have not been identified. One interesting concept, proposed by Malliani,[34] is that peripheral pain may be considered a "specific" sensation, with well defined nociceptors, whereas cardiac pain is more dependent on an "intensity" mechanism relating to the spatiotemporal pattern of cardiac algogenic stimuli, and hence might be less susceptible to the influence of circulating endorphin concentrations. In addition, differing central mechanisms for somatic and cardiac pain perception are described. Cells in the posterior part of the principal sensory nucleus of the thalamus may be involved in cardiac pain perception, as these are known to respond to cardiac sympathetic afferent stimulation, and electrical stimulation in this area can induce symptoms almost identical to perceived angina symptoms.

EFFECTS OF NALOXONE

We did not observe changes in either angina or peripheral pain thresholds after administration of naloxone at doses expected to antagonise the effects of both centrally mediated opioid release and circulating plasma β endorphins. Circulating concentrations of β endorphin were low, but later increased during naloxone infusion, consistent with effective opioid receptor blockade. Our findings are consistent with those of Ellestad *et al*[35] and Weidinger *et al*[20] who were unable to induce angina in patients with silent ischaemia after administration of lower doses of naloxone (2 mg and 1.2 mg, respectively), and of Marchant *et al*,[22] who were unable to induce angina by administration of naloxone to patients with asymptomatic ischaemia. However, these investigators were able to demonstrate a significant effect of naloxone on the electrical pain threshold but not on angina threshold in patients with symptomatic ischaemia undergoing exercise treadmill testing using a higher range dose of naloxone (6 mg followed by 0.1 mg/min during the exercise test). In addition, Droste *et al* reported that two of 10 patients with silent ischaemia developed anginal symptoms at a lower threshold after administration of naloxone in the higher dose range (6 mg intravenously).[21] It is not possible from these studies, however, to differentiate between central or circulating opioid effects.

LIMITATIONS

Several limitations of this study should be considered. First, the trend towards a rise in plasma β endorphin concentrations following naloxone administration, and towards a decrease in peripheral pain threshold, might have reached statistical significance with a much larger patient population, as such effects have previously been reported[22]; similarly, a minor influence of plasma β endorphins on angina threshold might be detectable by studying a considerable larger patient population, although any such changes would remain an order of magnitude less than the observed effects on somatic pain perception and are unlikely to be of clinical significance. Second, determinations of pain thresholds are, by their nature, subjective and affected by habituation, although our randomisation of the order of study conditions should have controlled for

such effects. Third, training effects with repeated exercise treadmill testing may have occurred.[36]

CONCLUSIONS

Our study suggests that increases in circulating plasma β endorphin concentrations can modulate somatic pain perception with little or no clinically significant effect on angina threshold in patients with symptomatic angina of effort. This peripheral somatic effect would be in addition to the known central influences of opioid and non-opioid analgesia systems on both peripheral and cardiac pain perception. A clinical inference which might be drawn from this study is that any role of β endorphins in the pathogenesis of silent ischaemia would be more likely mediated by central opioid mechanisms than by acute changes in circulating plasma β endorphins.

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